REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1, 3-4, 7-8, 10-23, 32-33, 50-52, and 53-54 will be pending in this application and presented for examination. Claim 1 has been amended. Claims 53-54 are newly added and read on the current election. No new matter has been entered with the foregoing amendments and newly added claims. Reconsideration in view of the foregoing amendments and following remarks is respectfully requested.

I. FORMALITIES

Applicants have included a copy of a Communication under 71(3) EPC from the European Patent Office, for the corresponding European Application, which is an intent to grant. A copy of the allowed claims are also enclosed for the convenience of the Examiner. The Communication indicates that another respected patent office has independently reviewed and examined the application and claims under high standards of patentability and allowed the case.

Claim 1 has been amended to delete the term "corresponds" and the SEQ ID NOs have been put into a Markush group. In addition, claim 1 has been amended with features of original claim 2.

Claims 53-54 are newly added and find support in claims 50-51. Applicants believe claims 53 and 54 are clearly allowable.

The obvious error in the Specification has been updated as requested by the Examiner.

Applicants respectfully request that the amendment and new claims be entered.

II. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner has maintained the rejection of claims 1, 3, and 32-33 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection. Each of the Examiner's comments is addressed in turn.

a) With regard to claim 3, the Examiner alleges that the claim recites that the peptide is *modified* from a particular sequence, making the claim indefinite.

However, as the Examiner is well aware, each limitation of the independent claim is incorporated by reference into the dependent claim (35 USC § 112, 4th paragraph). Thus, the term *modified* is such that the peptide is modified according to the features of claim 1. In other words, the modifications that claim 3 recites are the same modifications of claim 1. As such, Applicants respectfully request that the Examiner withdraw the rejection.

b) With respect to claim 1, the Examiner alleges that the term "*corresponds*" can mean similar instead of identical. In order to expedite prosecution of the present application, Applicants have amended claim 1 to remove the "*corresponds*" language, rendering this rejection moot.

c) With respect to the term "halogenated" in claim 1, the Examiner alleges that it is unclear whether the halogenated amino acid is inserted somewhere in the sequence or if the halogenated amino acid is substituted for another amino acid. Applicants respectfully traverse the rejection.

The claims language recites :

> ... a thioether bond between a substituted cysteine residue at said first or said second amino acid and a *halogenated* amino acid residue at the other position, either directly or via a spacer group.

Applicants assert that the claim language is clear and definite to a skilled artisan. The halogenated amino acid in merely one of the two amino acids that makes up the intrapeptide cyclization. For example, the first amino acid can be a cysteine residue and the second amino acid can be amino acid, which has been halogenated. Alternatively, the first amino acid can be halogenated and the second amino acid can be a cysteine. As such, Applicants respectfully request that the Examiner withdraw the rejection.

d) With respect to the term "spacer group," the Examiner alleges that it is unclear whether the term "spacer group" is intended to refer generally to a covalent bond or specifically to a thioether bond or to a disulfide bond. Applicants respectfully traverse the rejection.

With reference to the claim language in "c" above, a skilled artisan would readily understand that the spacer group between the first and second amino acids must allow the cyclic peptide to bind to its biological target. This fact plus the example of a spacer group on page 13, lines 17-18, Applicants submit that the term spacer group is clear and definite. As such, Applicants respectfully request that the Examiner withdraw the rejection.

e) The Examiner states that the instant claims refer to positions in a range of 2 and 8 and in a range of 21 and 26 of 'said peptide sequences.' However, according to the Examiner, the claims refer to 'synthetic monomeric, cyclic B-chain peptide' as well as SEQ ID NO:1 for example. Since SEQ ID NO:1 is not cyclic, the 'synthetic monomeric, cyclic B-chain peptide' is not the equivalent of SEQ ID NO: 1. The Examiner then says it is unclear if 'said peptide sequences' is in reference to the cyclic (or modified) peptide or if 'said peptide sequences' is in reference to specific SEQ ID NOs. The Examiner states that if the reference is to the cyclic (or modified) peptide it is unclear if the cyclic portion is numbered and counted clockwise or counterclockwise. In response, Applicants respectfully traverse the rejection.

A skilled artisan would readily understand that the instant claims recite a range of positions from 2 to 8 and from positions 21 to 26 of 'said peptide sequences," which are the claimed peptides. As the Examiner stated, SEQ ID NOs 1, 2, 3, 7, 8, 9, and 10 are not cyclic. However, the position are numbered left to right. The claim language recites:

> ...between a first amino acid within a range of amino acid positions 2 and 8 and a second amino acid within a range of positions 21 and 26 of each of said peptide sequences ...

FIG 3 has three exemplified synthetic monomeric, cyclic B-chain peptides as currently claimed. These peptides have SEQ ID NOs 11, 12 and 13. The sequences have the position numbers in the sequence listings. A skilled artisan would readily recognize residues in positions 2 through 8 and positions 21 through 26, are simply numbered starting from their N-terminus and ending at their C-terminus. As such, Applicants respectfully request that the Examiner withdraw the rejection.

f) The Examiner states that the claims refer to 'disulfide bond between two cysteine residues.' The claims also refer to positions 2 and 8 and 12 and 26. Since SEQ ID NO:1, for example, includes a cysteine residue at position 10, and it is unclear if such cysteine can be included in the disulfide bond. In response, Applicants respectfully traverse the rejection.

A skilled artisan would readily understand that position 10 is not within the range of residues 2 and 8 nor between the residues of 21 and 26. Accordingly, this position is not within the claimed language. As such, a skilled person would readily understand that the cysteine at position 10 is clearly not in this range. As such, Applicants request that the Examiner withdraw the rejection.

g) Finally, the Examiner states that the claims refer to 'monomeric' yet also refer to a cyclic peptide with a spacer. The Examiner notes that a peptide is necessarily a polymer unit including repeats of amino acids. Further, 'monomeric' in the context of cyclic peptides is unclear. In response, Applicants respectfully traverse the rejection.

Applicants are using an "art recognized" term to describe their invention. A skilled artisan would readily appreciate that the relaxin superfamily of proteins consist of an A-chain and a B-chain. The term "monomeric" B-chain, as a skilled artisan would appreciate, means only the B-chain is included in the claim. Moreover, one of skill in the art would understand that the "cyclic" nature of the monomeric B-chain adds in-part to the novelty of the claimed invention. Moreover, as explained more fully below, as *monomeric* B-chains do not occur cyclized in nature, the inventive claims clearly are statutory patentable subject matter.

As such, Applicants respectfully request that the Examiner withdraw all the 35 USC § 112, second rejections.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1 and 3 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In brief, the Examiner argues that that the examples do not represent the genus as claimed. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

As the Examiner is aware:

> [t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

The monomeric cyclic B-chain peptide are currently being claimed by a combination of structure and function totally in compliance with *Eli Lilly*. The written description requirement for a claimed genus is clearly satisfied. The claims recite the modification of merely 7 discrete starting molecules set forth by their structure i.e., SEQ ID NOs 1-3 and 7-10, to make the monomeric cyclic B-chain peptides. The claimed modifications conformationally constrain each of the claimed molecules. The conformational constraint is accomplished via various modification techniques such as the formation of a covalent bond between the side chains of the first and second amino acids or a disulfide bond between two cysteine residues, wherein the two cysteine residues are substituted for the first and said second amino acids, or a thioether bond between a substituted cysteine residue at the first or the second amino acid and a halogenated amino acid residue at the other position, either directly or via a spacer group. The first and second amino acid are well defined. The first amino acid is within a range of amino acid positions 2 and 8 and a second amino acid is within a range of positions 21 and 26 of each of the peptide sequences, as claimed.

A skilled artisan would readily recognize that the claims require the 7 amino acids sequences i.e., the B-chain monomers, be cyclized between two amino acids. The two amino acids are required to be within a range of amino acid positions 2 and 8 for the first amino acid and within a range of positions 21 and 26 as a second amino acid. Moreover, as amended, the 2 amino acid positions must be separated with an alpha-helix or beta-strand carbon separation distance of less than six angstroms.

The seven relaxin superfamily proteins now recited in amended claim 1 can be clearly divided into two related sub-groups, *relaxin proteins* on the one hand and *INSL proteins* on the other. Moreover, the application and claims recite no fewer than 3 examples of the inventive monomeric B-chain cyclic peptides. In this regard, the Examiner's attention is respectfully directed to Figure 3. As shown therein, starting B-chain SEQ ID NOs 2 and 7 are labeled "relaxin" and "INSL-3 B-chain." In addition, 3 claimed monomeric B-chain cyclic peptides are shown therein, i.e., "cRlx" ; "cINSL3a" and "cINSL3b." These molecules represent a representative number of species by actual reduction to practice of the genus now claimed. Figure 3 clearly provides examples of cyclic peptides produced in accordance with the claims for members of each subgroup, namely relaxin 1 and INSL3.

But there is more. The claimed genus is described by a representative number of species by actual reduction to practice, as well as by functional characteristics coupled with a known or disclosed correlation between function and structure. This description is sufficient to show Applicants were in possession of the claimed genus. The claims require that the monomeric, cyclic B-chain peptides as claimed bind to a biological target of the relaxin superfamily protein i.e., IGFR-I, IGFR-II, LGR7 or LGR8. These receptors are well known in the art, are well characterized and their binding characteristics are also known. The level of skill in the skill and knowledge in the art is such that a skilled artisan would readily recognize that Applicants were in possession of the claimed genus. As such, Applicants request that the rejection be withdrawn.

IV. REJECTION UNDER 35 USC § 101

The Examiner maintained the rejections of claims 1, 3 and 32-33 under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. In response, Applicants respectfully traverse the rejection.

Despite having amended the claims to recite "a synthetic" peptide, the Examiner states:

> [a]lthough Applicants argue that the word 'synthetic' is used in the claims, by definition 'synthetic' refers to something that has been

> synthesized. Schwabe teach that the relaxin-like factor (for example as shown in Figure 1) is from a human source (human Ley I-L) (column 3, lines 7-12 and column 2 lines 26-50). Since Schwabe teach that the relaxin-like factor is a naturally occurring peptide *it* has *been synthesized by a natural process and thus is 'synthetic'*. [emphasis added]. Further, "synthetic" does not imply non-naturally occurring. Synthetic implies a mode of making a peptide. Incredibly, the Examiner states: A naturally occurring peptide made synthetically would still be a product of nature. There is no indication that the peptides of the current invention have been isolated or removed from a naturally occurring environment." [Emphasis added]

Applicants respectfully traverse the Examiner's statement. The term "synthetic," means that it is *not* a product of nature. The term synthetic means the peptide is for example, chemically synthesized. It is not a product of nature. Contrary to the Examiner's statement, a naturally occurring peptide made chemically is *not* a product of nature.

As the Supreme Court has recognized, Congress chose the expansive language of 35 U.S.C. §101 so as to include "anything under the sun that is made by man" as statutory subject matter. *Diamond v. Chakrabarty*, 447 U.S. 303, 308-09, 206 USPQ 193, 197 (1980). Moreover, a skilled artisan would readily appreciate that since B-chain monomeric peptides do not occur cyclized in nature, the claimed invention is *prima facie* statutory subject matter. A *synthetic peptide* meets the requirements of 35 U.S.C. § 101, as it is *not* a product of nature because it has been manufactured by a human. Contrary to the Examiner's statement, a synthetic peptide *is non-naturally* occurring. As recited in the first and second definition of the term "synthetic" below.

In this regard, the Examiner's attention is directed to the dictionary definition of the term "synthetic" which means non-naturally occurring to peptide chemists.

> 1. of, or pertaining to synthesis. 2 (of a substance or material) chemically synthesized as opposed to prepared from natural recognizable natural materials. Such a product is identical chemically to that isolated from the natural source.

Using the dictionary definition of "synthetic," a skilled artisan would readily recognize that the peptide is chemically synthesized and not naturally occurring.

However, there is more. Applicants searched the PTO Website on November 2, 2009 with key words "synthetic peptide" in the claims and got 427 hits. For example, claim 1 of U.S. Patent No. 7,399,825 recites:

> A *synthetic peptide* molecule consisting of a portion of SEQ. ID. NO.: 1 which contains SEQ. ID. NO.: 2 beginning at the N-terminal.

Of the 427 patents, the following seven issued patents have the Examiner's supervisor, Examiner Cecilia Tsang, as the Primary Examiner, US Patent Nos:

7,402,564 Synthetic peptide amides

7,319,089 Maurocalcine, analogues thereof and their therapeutical uses

7,232,881 Peptide containing Ser-Ser-Ser-Arg

7,199,103 Synthetic compounds and compositions with enhanced cell binding

5,965,701 Kappa receptor opioid peptides

5,837,686 Peptides and antibodies for treatment of rheumatoid arthritis

5,726,153 Synthetic peptides for arterial imaging

A synthetic peptide means it is non-naturally occurring and therefore, like the other issued 427 US Patents, the present claims meet the requirement of 35 USC § 101. Accordingly, the recited subject matter is patent eligible. As such, Applicants respectfully request that the Examiner withdraw the rejection.

V. FIRST REJECTION UNDER 35 USC § 102(b)

The Examiner has maintained the rejection of claims 1 and 3 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,911,997 ("Schwabe *et al.*"). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner states:

> ...in Figure 1 of Schwabe the B-chain of RLF is linked with the A-chain of RLF. In particular, residue 10 (i.e. Cys) and residue 22 (i.e. Cys) of the *B-chain are linked to the A-chain.* Together, residues 10-22 of the B chain of RLF form a cyclic structure with residues 11-24

> of the A chain of RLF. In other words the sequence of the cyclic structure includes residues 10-22 of the B chain of RLF followed by residues 24-11 of the A chain of RLF (i.e. CGHHFVRALVRVCCLTLLDQQTCGSLC). Schwabe teach compositions of RLF (column 3, lines 7-12) and teach pharmaceutical compositions of RLF with carriers for example (column 8, lines 37-55) as recited in claims 32-33 of the instant invention. [Emphasis added].

Further, the Examiner states:

> Applicants argue that the claims refer to a monomer and the art refers to a dimer, which is defined as a molecule consisting of subunits. First, it is noted that a peptide is necessarily a polymer unit including subunits of amino acids. The instant specification provides no specific definition of 'monomeric'. There is no definition provided in the instant specification of 'monomeric' in the context of cyclic peptides. Thus the peptides as claimed can not be monomeric based on the applicants' cited definition. Since a peptide is necessarily a polymer unit including subunits of amino acids, applicants' cited definition is evidence that the claims are unclear and confusing. Further, 'monomeric' in the context of cyclic peptides or disulfide bonded peptides is unclear. Further, it is noted that the claims refer to 'spacer groups'. When the cross-link is connected via a spacer that is a sequence of amino acids, it is unclear what differentiates a cyclic monomeric peptide from a cyclic dimeric peptide from a cyclic peptide.

A skilled artisan would readily recognize that the claim language of the subject application recites "art recognized" terminology. The art is clear. In nature, SEQ ID NOs 1, 2, 3, 7, 8, 9, and 10, would appear as dimers of an A-chain and a B-chain, whereas the recited SEQ ID NOs are merely the B-chains. A skilled artisan would readily recognize these B-chains as a monomer, *i.e.*, a monomeric B-chain peptide. A skilled artisan would readily recognize that a cyclized B-chain is a *monomeric cyclic B-chain peptide*.

Unlike the heterodimer of Schwabe *et al.* having both an A-chain and a B-chain, the claimed invention is a monomer, *i.e.*, a single B-chain subunit. Schwabe teaches two chains both an A-chain and a B-chain (the Examiner's attention is respectfully directed to the legend for FIG. 2 in column 3, lines 49-60), whereas the claimed monomeric peptide is drawn to the B-chain only.

As discussed in the corresponding European Patent prosecution:

By way of reference to enclosed claim 1, the claims are now clearly directed towards an analogue of a B-chain of a relaxin superfamily member, which is both monomeric and cyclic. In this regard, the claim also stipulates that the analogue is produced by selecting at least a first and a second amino acid residue with an alpha-helix or beta-strand carbon separation distance of less than 6 angstroms and cross-linking same such that the resulting analogue is conformationally constrained. It is our respectful submission that none of the prior art documents on the table clearly and unambiguously discloses the monomeric and cyclic peptide analogues falling within the scope of enclosed claim 1.

With regard to Schwabe (referred to as D1) it was argued:

In particular, D1 relates to relaxin analogues, which analogues comprise a combination of relaxin A and B-chains, wherein the free-cysteine reduced forms of the A and B chains are mixed under defined conditions (aqueous medium, pH between 7 and 12 and mildly denaturing the B-chain). As a consequence, the resulting analogues produced in accordance with the teaching of D1 are *multimeric* as opposed to *monomeric*. Furthermore, neither are the resulting analogues cyclic. We would also add that D1 is wholly silent with respect to the production of monomeric, cyclic B-chain relaxin analogues and there is no suggestion whatsoever of the modifications recited by the present claim set.

Under MPEP § 2131:

[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

A skilled artisan would readily recognize that Schwabe simply do not teach a B-chain of a relaxin superfamily member as claimed, which is both *monomeric* and *cyclic* as is now claimed. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the rejection.

VI. SECOND REJECTION UNDER 35 USC § 102(b)

The Examiner has now rejected claims 1, 3, and 32-33 under 35 U.S.C. § 102(b) as allegedly being anticipated by Bullesbach *et al.*, (*Chem Pept Proteins Proc* 1982, pp 327-335). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner states: Bullesbach teach the preparation of the B-chain of an insulin peptide (Figure 2, page 328, last paragraph) in which the cysteine residues at positions 7 and 19 are cross-linked. The Examiner further states:

> ...that since the claims state that the peptide 'corresponds' to particular sequences and the definition of correspond is 'similar', any similarity (the presence of amino acids, for example) is deemed sufficient to 'correspond'. Since it is unclear if modifications can include insertions, deletions, etc. and it is unclear if the numbering is in reference to a modified or unmodified sequence the claims are given the broadest reasonable interpretation such that any peptide that includes the cyclization modification meets the claim limitations including those which use a naturally present cysteine.

Continuing the Examiner states:

> Bullesbach specifically show a cross-link between amino acids (Figure 2). Since peptides are necessarily polymeric, such peptides are interpreted as meeting the claim limitations. Further, section 2111.01 I of the MPEP states that the claims should be given the broadest reasonable interpretation in light of the specification. In the instant case, the specification (page 25 lines 27-31, Figure 3 'cINSL3b', claim 51) refer to a specific peptide. The specification states that the peptide is INSL3-based. The sequence of the b-chain of INSL3 is provided by SEQ ID NO:7 and is:PTPEMREKLCGHHFVRALVRVCGGPRWSTEA. Thus SEQ ID NO:7 is 31 amino acids in length. cINSL3b is 27 amino acids in length. Thus it is consistent with the specification that 'correspond to' is not the equivalent of 'identical to'. Further, SEQ ID NO:7 includes the sequence LCGHH (positions 9-13) while the corresponding sequence in cINSL3b is LSGRH.

Bullesbach *et al.* teach combined enzymatic and chemical synthesis methods to make proinsulin. The B-chain of proinsulin in shown in FIG 2 of Bullesbach *et al.* However,

claim 1 as previously amended deleted the term "insulin." In fact, mature insulin has 39 fewer amino acids than proinsulin. Four amino acids are removed, and the remaining 35 amino acids form the C-peptide. The C-peptide is abstracted from the center of the proinsulin sequence; the two other ends (the B chain and A chain) remain connected by disulfide bonds.

None of SEQ ID NOs 1-3, 7, and 8-10 in claim 1 represents the B-chain of proinsulin. Moreover, position 19 is outside the claimed range of the second amino acid. Applicants respectfully note that the numbering of this B-chain of proinsulin is numbered in the art recognized fashion, starting at the N-terminus and ending at the C-terminus.

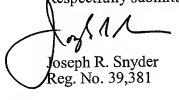
As each and every element of the claims is not found in the cited art, the claims are not anticipated. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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